IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

IN RE: '318 PATENT INFRINGEMENT LITIGATION	))))	C.A. No. 05-356-KAJ (consolidated)

NOTICE OF DEPOSITION UNDER FED. R. CIV. P. 30(b)(6)
TO MYLAN PHARMACEUTICALS INC. AND MYLAN LABORATORIES, INC.

PLEASE TAKE NOTICE that on March 15, 2006 commencing at 9:00 a.m., at the offices of Covington & Burling, 1201 Pennsylvania Avenue, N.W., Washington, D.C. 20004, Plaintiffs Janssen Pharmaceutica N.V., Janssen, L.P. and Synaptech, Inc. (collectively, "Plaintiffs" or "Janssen") will take the deposition upon oral examination of Defendants Mylan Pharmaceuticals Inc. and Mylan Laboratories Inc. (collectively, "Mylan") pursuant to Rule 30(b)(6) of the Federal Rules of Civil Procedure. This deposition upon oral examination will be conducted before an officer authorized to administer oaths and will be recorded by stenographic and videographic means.

Plaintiffs serve this Notice without waiver of its objections to the deficiencies in Mylan's document production and other discovery responses concerning the subject matter of the instant Notice, and reserve the right to continue this deposition as necessary in light of any subsequent document production by Mylan.

Plaintiffs will take this deposition upon oral examination through one or more officers, directors, managing agents or other persons designated by Mylan pursuant to Rule 30(b)(6) of the Federal Rules of Civil Procedure as the person(s) knowledgeable to testify on Mylan's behalf concerning the topics identified in Schedule A. Mylan is requested to provide counsel for Plaintiffs with the identity of the individual(s) who will testify regarding each

topic at least one week in advance of the deposition. The deposition will continue from day to day until completed with such adjournments as to time and place as may be necessary. You are invited to attend and examine the witness(es).

ASHBY & GEDDES

/s/ Lauren E. Maguire

Steven J. Balick (I.D. #2114)
John G. Day (I.D. #2403)
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One Johnson & Johnson Plaza
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Fax: 732-524-5866

Dated: February 21, 2006
166717.1

SCHEDULE A

Definitions

1. As used herein, "Mylan" shall mean Defendants Mylan Pharmaceuticals Inc. and Mylan Laboratories Inc. and all of Mylan's corporate parents, corporate predecessors and past or present subsidiaries, affiliates, divisions, departments, officers, directors, principals, agents and employees.

2. As used herein, "Mylan's ANDA" shall mean Mylan's Abbreviated New Drug Application Number 77-590.

3. As used herein, "the Generic Product" shall mean the proposed generic galantamine product that is the subject of Mylan's ANDA.

4. As used herein, "the '318 patent" shall mean United States Patent No. 4,663,318.

5. As used herein, "document" shall have the full meaning ascribed to it by the Federal Rules of Civil Procedure and shall include any means for retaining information.

6. As used herein, "FDA" shall mean the United States Food and Drug Administration.

7. As used herein, "Paragraph IV notice" refers to Mylan's April 27, 2005 letter to Plaintiffs attached hereto as Exhibit 1.

8. "Person" and "persons" mean any natural person and any business, legal, corporate, or governmental entity, association, or organization.

9. "Alzheimer's Disease" means any diagnosis, illness, or ailment described as being of the Alzheimer's type, including without limitation Senile Dementia of the Alzheimer's Type, Alzheimer's Dementia, and/or Alzheimer's Disease.

10. "Galantamine" includes without limitation galantamine, galanthamine, and any salt of galatamine, such as galantamine hydrobromide.

Topics of Examination

1. Mylan's Paragraph IV notice including, without limitation, the meaning of, basis for, and any evaluation or analysis concerning the statement set forth in the letter that the "'318 patent[] will not be infringed by the commercial manufacture, use or sale of the drug products described in Mylan's ANDA and/or such patents are invalid."

2. Any evaluation, consideration or discussion conducted by Mylan to develop the Generic Product, including the names and responsibilities of all persons who were involved in the evaluation, consideration or discussion by Mylan to develop the Generic Product.

3. The decision to file an application with the FDA seeking approval to manufacture and sell a drug product containing galantamine.

4. Any evaluation, consideration or discussion conducted by Mylan to market the Generic Product, including the names and responsibilities of all persons who were involved in the evaluation, consideration or discussion by Mylan to market the Generic Product.

5. The benefits, including revenues and profits, that Mylan projects, anticipates, expects, or forecasts it will obtain should Mylan's ANDA receive approval from the U.S. Food and Drug Administration.

6. Marketing strategies, marketing plans, and projected sales for Mylan's Generic Product.

7. Each and every contribution and/or input that Mylan, or any employee or agent of Mylan, has made to the preparation, decision to file, filing and/or prosecution of

Mylan's ANDA, including: (a) any information relating to regulatory procedures and strategies for obtaining regulatory approval of the Generic Product of Mylan's ANDA; (b) any information comprising, relating to or contained in the 21 U.S.C. § 355(j)(2)(A)(vii)(IV) certifications submitted in connection with Mylan's ANDA; and (c) any information comprising, relating to or contained in the statements of factual and legal basis for invalidity, unenforceability, and/or noninfringement included with the notice of these certifications.

8. The factual basis for Mylan's proposed assertion that its ANDA is indicated for the treatment of mild to moderate Alzheimer's disease.

9. The circumstances in which Mylan first became aware of galantamine as a treatment for Alzheimer's disease, including but not limited to the date in which this occurred and the people involved.

10. The circumstances in which Mylan first became aware of the '318 patent, including but not limited to the date in which this occurred and the people involved.

11. Any consideration or evaluation to develop a drug product containing galantamine for the treatment of Alzheimer's disease conducted by or on behalf of Mylan.

12. Identification of all individuals, whether employees of Mylan or third parties, having a role in the consideration or evaluation by Mylan of developing a drug product containing galantamine for the treatment of Alzheimer's disease that is the subject of Topic 10.

13. Any effort to develop any drug product other than the Generic Product set forth in Mylan's ANDA for the treatment of Alzheimer's disease conducted by or on behalf of Mylan.

14. Identification of all individuals, whether employees of Mylan or third parties, having a role in the research, development or testing of such a treatment responsive to Topic 12 and a description of those roles.

15. The factual and legal bases for Mylan's Second Defense (invalidity).

16. The factual and legal bases for Mylan's Second Claim for Relief (declaratory judgment of invalidity) according to its proof elements, including an element-by-element comparison of each asserted claim of the '318 patent to the prior art Mylan relies upon and the motivation of one of skill in the art to combine any references under 35 U.S.C. §103, as well as a description of any non-prior art defenses such as lack of enablement, insufficient written description, failure to disclose best mode, or claim indefiniteness under 35 U.S.C. § 112.

17. The identity and location of documents and things concerning the foregoing topics.

18. Mylan's document retention policies from 1986 to the present.

19. Persons knowledgeable about the subject matter of the foregoing topics.

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EXHIBIT 1

RAKOCZY MOLINO MAZZOCHI SIWIK LLP

6 WEST HUBBARD STREET
SUITE 500
CHICAGO, IL 60610
www.rmmslegal.com

312-527-2157 main phone
312-527-4205 main fax

April 27, 2005

Via FedEx® International Priority Service and Registered U.S. Mail Air Letter Post, Return Receipt Requested; and FedEx® Priority Overnight Service and Certified U.S. Mail, Return Receipt Requested

Chief Executive Officer
Janssen Pharmaceutica N.V.
Turnhoutseweg 30
B-2340
Beerse, Belgium

Chief Executive Officer
Janssen Pharmaceutica
1125 Trenton-Harbourton Road
Titusville, New Jersey 08560

Chief Executive Officer
Synaptech Inc.
225 Broadway, 42nd Floor
c/o Schwartz & Salomon
New York, New York 10007

CONFIDENTIAL

Re: Notification of Certification of Noninfringement and/or Invalidity for U.S. Patent Nos. 6,099,863; 6,358,527 B1; and 4,663,318 Pursuant to § 505(j)(2)(B)(iv) of the Federal Food, Drug, and Cosmetic Act

Dear Madam or Sir:

On behalf of Mylan Pharmaceuticals Inc. ("Mylan"), pursuant to § 505(j)(2)(B)(iv) of the Federal Food, Drug, and Cosmetic Act and 21 C.F.R. § 314.95, we hereby provide notice of the following information to: Janssen Pharmaceutica N.V. ("Janssen"), the owner of U.S. Patent Nos. 6,099,863 ("the '863 patent") and 6,358,527 B1 ("the '527 patent"), according to the records of the U.S. Patent and Trademark Office ("PTO"); Synaptech, Inc. ("Synaptech"), the owner of U.S. Patent No. 4,663,318 ("the '318 patent"), according to the records of the PTO; and Janssen Pharmaceutica ("Janssen Pharma"), the holder of approved New Drug Application ("NDA") No. 21-169 for Reminyl® (galantamine hydrobromide) Tablets 4 mg, 8 mg, and 12 mg, according to the records of the U.S. Food and Drug Administration ("FDA").

Pursuant to 21 C.F.R. § 314.95(c), Mylan requested and received from FDA permission to send this notice by additional means other than registered or certified mail. Specifically, Mylan requested that it be allowed to send this notice by Federal Express®. FDA granted Mylan's request prior to this notice being sent. Consequently, the operative date for determining the start of the 45-day clock under 21 U.S.C. § 355(j)(5)(B)(iii) began from the earliest receipt of this notice, as sent via Federal Express® or registered/certified mail, whichever is earlier.

I. Pursuant to 21 U.S.C. § 355(j)(2)(B)(iv)(I) and 21 C.F.R. § 314.95(c)(1), we advise you that FDA has received an Abbreviated New Drug Application ("ANDA") from Mylan for Galantamine Hydrobromide Tablets 4 mg, 8 mg, and 12 mg. The ANDA contains the required bioavailability and/or bioequivalence data from studies on the galantamine hydrobromide tablet drug products that are the subject of the ANDA. The ANDA was submitted under 21 U.S.C. § 355(j)(1) and (2)(A), with a paragraph IV certification to obtain approval to engage in the commercial manufacture, use or sale of Galantamine Hydrobromide Tablets 4 mg, 8 mg, and 12 mg before the expiration of the '863, '527, and '318 patents, which are listed in the Patent and Exclusivity Information Addendum of FDA's publication, *Approved Drug Products with Therapeutic Equivalence Evaluations* (commonly known as "the Orange Book").

II. Pursuant to 21 C.F.R. § 314.95(c)(2), we advise you that FDA has assigned Mylan's ANDA the number 77-590.

III. Pursuant to 21 C.F.R. § 314.95(c)(3), we advise you that the established name of the drug products that are the subject of Mylan's ANDA is Galantamine Hydrobromide Tablets 4 mg, 8 mg, and 12 mg.

IV. Pursuant to 21 C.F.R. § 314.95(c)(4), we advise you that the active ingredient in the proposed drug products is galantamine hydrobromide; the strengths of the proposed drug products are 4 mg, 8 mg, and 12 mg; and the dosage form of the proposed drug products is an oral tablet.

V. Pursuant to 21 C.F.R. § 314.95(c)(5), we advise you that the patents alleged to be not infringed and/or invalid in the paragraph IV certification are the '863, '527, and '318 patents, which are listed in the Orange Book in connection with Janssen Pharma's approved NDA No. 21-169 for Reminyl® (galantamine hydrobromide) Tablets 4 mg, 8 mg, and 12 mg. According to information provided by Janssen Pharma to FDA that is published in the Orange Book, the '863 patent will expire on or about June 6, 2017; the '527 patent will expire on or about June 6, 2017; and the '318 patent will expire on or about December 14, 2008.

VI. Mylan alleges, and has certified to FDA, that in Mylan's opinion and to the best of its knowledge, the '863, '527, and '318 patents will not be infringed by the commercial manufacture, use or sale of the drug products described in Mylan's ANDA and/or

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s are invalid. Therefore, pursuant to 21 U.S.C. § 355(j)(2)(B)(iv)(II) and 21 C.F.R.
(6), Mylan's detailed statement of the legal and factual basis for the paragraph IV
set forth in Mylan's ANDA is attached hereto and made a part hereof.

VII. Pursuant to 21 U.S.C. § 355(j)(5)(C), this notice letter includes an Offer of
l Access to Application. As required by § 355(j)(5)(C)(i)(III), Mylan offers to
nfidential access to certain information from its ANDA No. 77-590 for the sole and
purpose of determining whether an infringement action referred to in
(B)(iii) can be brought.

Section 355(j)(5)(C)(i)(III) allows Mylan to impose restrictions "as to persons
access, and on the use and disposition of any information accessed, as would apply
tective order been entered for the purpose of protecting trade secrets and other
al business information." That provision also grants Mylan the right to redact its
response to a request for Confidential Access under this offer.

As permitted by statute, Mylan imposes the following terms and restrictions on its
onfidential Access:

) Mylan will permit confidential access to certain information from its proprietary ANDA No. 77-590 to attorneys from one outside law firm representing Janssen, Janssen Pharma, and Synaptech (collectively, "Janssen"); provided, however, that such attorneys do not engage, formally or informally, in any patent prosecution for Janssen or any FDA counseling, litigation or other work before or involving FDA. Such information (hereinafter, "Confidential Mylan Information") shall be marked with the legend "CONFIDENTIAL."

2) The attorneys from the outside law firm representing Janssen shall not disclose any Confidential Mylan Information to any other person or entity, including Janssen employees, outside scientific consultants, and/or other outside counsel retained by Janssen, without the prior written consent of Mylan's outside litigation counsel, RAKOCZY MOLINO MAZZOCHI SIWIK LLP.

(3) As provided by § 355(j)(5)(C)(i)(III), Janssen's outside law firm shall make use of the Confidential Mylan Information for the sole and exclusive purpose of determining whether an action referred to in § 355(j)(5)(B)(iii) can be brought and for no other purpose. By way of example only, the Confidential Mylan Information shall not be used to prepare or prosecute any future or pending patent application by Janssen, or in connection with any filing to, or communication with, FDA relating to Mylan's ANDA No. 77-590. Janssen's outside law firm agrees to take all measures necessary to prevent unauthorized disclosure or use of the Confidential Mylan Information, and that all Confidential Mylan Information

shall be kept confidential and not disclosed in any manner inconsistent with this Offer of Confidential Access.

(4) The Confidential Mylan Information disclosed is, and remains, the property of Mylan. By providing the Confidential Mylan Information, Mylan does not grant Janssen and/or its outside law firm any interest in or license for the Confidential Mylan Information.

(5) Janssen's outside law firm shall, within thirty-five (35) days from the date that it first receives the Confidential Mylan Information, return to Mylan's outside litigation counsel, RAKOCZY MOLINO MAZZOCHI SIWIK LLP, all Confidential Mylan Information and any copies thereof. Janssen's outside law firm shall return all Confidential Mylan Information to RAKOCZY MOLINO MAZZOCHI SIWIK LLP before any infringement suit is filed by Janssen, if suit is commenced before this 35-day period expires. In the event that Janssen opts to file suit, none of the information contained in or obtained from any Confidential Mylan Information that Mylan provides shall be included in any publicly-available complaint or other pleading.

(6) Nothing in this Offer of Confidential Access shall be construed as an admission by Mylan regarding the validity, enforceability, and/or infringement of any U.S. patent. Further, nothing herein shall be construed as an agreement or admission by Mylan with respect to the competency, relevance, or materiality of any such Confidential Mylan Information, document, or thing. The fact that Mylan provides Confidential Mylan Information upon request of Janssen shall not be construed as an admission by Mylan that such Confidential Mylan Information is relevant to the disposition of any issue relating to any alleged infringement of the '863, '527, or '318 patent, or to the validity or enforceability of those patents.

(7) The attorneys from Janssen's outside law firm shall acknowledge in writing their receipt of a copy of these terms and restrictions prior to production of any Confidential Mylan Information. Such written acknowledgement shall be provided to Mylan's outside litigation counsel, RAKOCZY MOLINO MAZZOCHI SIWIK LLP.

(8) This Offer of Confidential Access shall be governed by the laws of the State of West Virginia.

Section 355(j)(5)(C)(i)(III) provides that any request for access that Janssen makes under this Offer of Confidential Access "shall be considered acceptance of the offer of confidential access with the restrictions as to persons entitled to access, and on the use and disposition of any information accessed, contained in [this] offer of confidential access" and that the "restrictions

and other terms of [this] offer of confidential access shall be considered terms of an enforceable contract." Thus, to the extent that Janssen requests access to Confidential Mylan Information, it necessarily accepts the terms and restrictions outlined above. Written notice requesting access under this Offer of Confidential Access should be made to:

William A. Rakoczy
RAKOCZY MOLINO MAZZOCHI SIWIK LLP
6 West Hubbard Street, Suite 500
Chicago, Illinois 60610
Tel: (312) 222-6301
Fax: (312) 222-6321
wrakoczy@rmmslegal.com

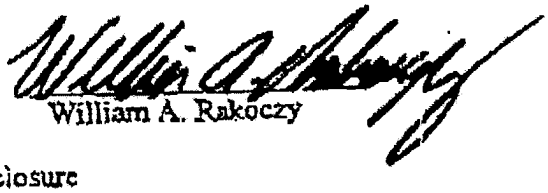
By providing this Offer of Confidential Access to Application, Mylan maintains the right and ability to bring and maintain a Declaratory Judgment action under 28 U.S.C. § 2201 *et seq.*, pursuant to 21 U.S.C. § 355(j)(5)(C).

The name and address of the agent in the United States authorized to accept service of process for Mylan, limited to commencement of a patent infringement suit based on this notification of certification, is:

William A. Rakoczy
RAKOCZY MOLINO MAZZOCHI SIWIK LLP
6 West Hubbard Street, Suite 500
Chicago, Illinois 60610
Tel: (312) 222-6301
Fax: (312) 222-6321
wrakoczy@rmmslegal.com

Very truly yours,

RAKOCZY MOLINO MAZZOCHI SIWIK LLP

By: 
William A. Rakoczy

Enclosure

Detailed Factual and Legal Basis for Mylan's Paragraph IV Certification that U.S. Patent Nos. 6,099,863; 6,358,527 B1; and 4,663,318 Will Not Be Infringed and/or Are Invalid

I. Introduction.

Pursuant to § 505(j)(2)(B)(iv)(II) of the Federal Food, Drug, and Cosmetic Act and 21 C.F.R. § 314.95(c)(6), this document is the detailed factual and legal basis for the paragraph IV certification of Mylan Pharmaceuticals Inc. ("Mylan") that, in its opinion and to the best of its knowledge, U.S. Patent Nos. 6,099,863 ("the '863 patent"), 6,358,527 B1 ("the '527 patent"), and 4,663,318 ("the '318 patent") will not be infringed by the commercial manufacture, use or sale of the drug products described in Mylan's ANDA No. 77-590, and/or such patents are invalid. Mylan reserves all rights to raise any additional defenses relating to invalidity, unenforceability, and noninfringement should litigation ensue.

II. Mylan's ANDA Product.

Mylan's ANDA product is an oral tablet containing galantamine hydrobromide as the active pharmaceutical ingredient in 4 mg, 8 mg, and 12 mg strengths (hereinafter, "Mylan's ANDA Product"). Mylan's ANDA Product does not contain or use any form of lactose. Nor does Mylan's ANDA Product contain a diluent or any other excipient made of a spray-dried mixture of 75% lactose monohydrate and 25% microcrystalline cellulose.

III. Legal Standards.

A. Patent Infringement.

A patent infringement analysis consists of two steps: (1) determining the scope of the claims, a legal issue for the court; and (2) comparing the accused product to the claims, a factual question. *Carroll Touch, Inc. v. Electro Mech. Sys., Inc.*, 15 F.3d 1573, 1576 (Fed. Cir. 1993). A claim may be infringed either: (1) literally; or, (2) under the judicially-created doctrine of equivalents. *See id.* Moreover, because a dependent claim incorporates all of the elements and limitations of the independent claim on which it depends, a dependent claim cannot be infringed unless each and every element of the underlying independent claim is also infringed. 35 U.S.C. § 112; *Forest Labs., Inc. v. Abbott Labs.*, 239 F.3d 1305, 1310 (Fed. Cir. 2001).

1. Claim Construction.

"It is axiomatic that the claims mark the outer boundaries of the patent right to exclude." *AstraZeneca AB v. Mut. Pharm. Co.*, 384 F.3d 1333, 1336 (Fed. Cir. 2004). The "goal of claim construction is to determine what an ordinary artisan would deem the invention claimed by the patent, taking the claims together with the rest of the specification." *Id.* at 1337 (citation omitted); *see also DeMarini Sports, Inc. v. Worth, Inc.*, 239 F.3d 1314, 1322 (Fed. Cir. 2001) (noting that claim construction "is simply a way of elaborating the normally terse claim language in order to understand and explain, but not to change, the scope of the claims" (internal quotations and citation omitted)).

The intrinsic evidence, including the claims, the specification, and the prosecution history, is the primary source for determining claim meaning. *See AstraZeneca*, 384 F.3d at 1336; *Markman v. Westview Instruments Inc.*, 52 F.3d 967, 979-80 (Fed. Cir. 1995) (en banc), *aff'd*, 517 U.S. 370 (1996). The claim construction inquiry begins with the plain and ordinary meaning of the claims, which define the scope of the right to exclude. *See Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996). "When construing patent claims, there is a heavy presumption that the language in the claim carries its ordinary and customary meaning amongst artisans of ordinary skill in the relevant art at the time of the invention." *Housey Pharms., Inc. v. AstraZeneca UK Ltd.*, 366 F.3d 1348, 1352 (Fed. Cir. 2004) (internal quotations and citations omitted).

A patentee may assign a claim term a meaning "other than its ordinary and accustomed meaning, . . . if the patentee has chosen to be his or her own lexicographer by clearly setting forth an explicit definition for a claim term." *Johnson Worldwide Assocs., Inc. v. Zebco Corp.*, 175 F.3d 985, 989 (Fed. Cir. 1999) (examining the scope of the term "reading" through its use by the patentee throughout the specification). However, if he or she intends to ascribe a meaning to a term other than its ordinary meaning, a clear and unambiguous demonstration of that meaning must be found in the specification. *See Markman*, 52 F.3d at 979-80; *Scherting Corp. v. Amgen Inc.*, 222 F.3d 1347, 1353 (Fed. Cir. 2000). The Federal Circuit has made clear that rigid formalism is not required. *See AstraZeneca*, 384 F.3d at 1339 (rejecting argument that lexicography requires rigid formalism and explicit statements of definition). Lexicography does not require "a statement in the form 'I define ____ to mean ____,'" but rather can be accomplished in a more subtle manner or even by implication. *Id.*; *see also Bell Atl. Network Servs., Inc. v. Covad Communications Group, Inc.*, 262 F.3d 1258, 1268 (Fed. Cir. 2001) ("[A] claim term may be clearly redefined without an explicit statement of redefinition. . . . [T]he specification may define claim terms 'by implication' such that the meaning may be 'found in or ascertained by a reading of the patent documents.'" (citation omitted)).

The specification also should be consulted to determine whether the patentee has disavowed or relinquished claim scope. *See SciMed Life Sys., Inc. v. Advanced Cardiovascular Sys.*, 242 F.3d 1337, 1341 (Fed. Cir. 2001) ("Where the specification makes clear that the invention does not include a particular feature, that feature is deemed to be outside the reach of the claims of the patent, even though the language of the claims . . . might be considered broad enough to encompass the feature in question."); *AstraZeneca*, 384 F.3d at 1340 ("Where the general summary or description of the invention . . . criticizes other products . . . that lack that same feature, this operates as a clear disavowal of these other products . . . ." (citation omitted)).

In addition, a patentee cannot recapture in litigation a claim scope surrendered during prosecution of the patent, either by amendment or argument. *See Pharmacia & Upjohn Co. v. Mylan Pharms., Inc.*, 170 F.3d 1373, 1376-77 (Fed. Cir. 1999). "Claims may not be construed one way in order to obtain their allowance and in a different way against accused infringers." *Southwall Techs., Inc. v. Cardinal IG Co.*, 54 F.3d 1570, 1576 (Fed. Cir. 1995) (citation omitted).

2. **Comparison of the Accused Product to the Properly Construed Claims.**

(a) **Literal Infringement.**

Literal infringement requires a patentee to prove that every limitation of the asserted claim is literally met by the accused product. *Energon GmbH v. Int'l Trade Comm'n*, 151 F.3d 1376, 1384 (Fed. Cir. 1998); *see also Amhil Enters. Ltd. v. Wawa, Inc.*, 81 F.3d 1554, 1562 (Fed. Cir. 1996) (recognizing that literal infringement occurs when "the properly construed claim reads on the accused device exactly"). The failure to meet even a single element within a claim mandates a finding that the accused product does not literally infringe the patent. *Laitram Corp. v. Rexnord, Inc.*, 939 F.2d 1533, 1535 (Fed. Cir. 1991).

(b) **Doctrine of Equivalents.**

Infringement under the doctrine of equivalents requires the patentee to show, for each claim asserted, the presence of each and every claim element or its substantial equivalent in the accused device. *See Warner-Jenkinson Co. v. Hilton Davis Chem. Co.*, 520 U.S. 17, 40 (1997); *Wolverine World Wide, Inc. v. Nike, Inc.*, 38 F.3d 1192, 1199 (Fed. Cir. 1994); *see also Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 U.S. 722, 732-33 (2002). An equivalent of a missing claim element or limitation is found only if "'insubstantial differences' distinguish the missing claim element from the corresponding aspects of the accused [product]." *Abbott Labs. v. Novopharm Ltd.*, 323 F.3d 1324, 1329 (Fed. Cir. 2003) (citation omitted).

However, the scope and application of this doctrine is limited. The Supreme Court has warned that "[i]t is important to ensure that the application of the doctrine, even as to an individual element, is not allowed such broad play as to effectively eliminate that element in its entirety." *Warner-Jenkinson*, 520 U.S. at 29. Under this "all elements rule, there can be no infringement under the doctrine of equivalents if even one limitation of a claim or its equivalent is not present in the accused device." *Lockheed Martin Corp. v. Space Sys./Loral, Inc.*, 324 F.3d 1308, 1321 (Fed. Cir. 2003) (citation omitted). In addition, the scope of permissible equivalents cannot encompass or ensnare what is already in the prior art. *See Marquip, Inc. v. Fosber Am., Inc.*, 198 F.3d 1363, 1367 (Fed. Cir. 1999). Likewise, under the doctrine of prosecution history estoppel, an equivalent cannot be extended to include subject matter surrendered by the patentee either in amendments to overcome patentability rejections or in arguments to secure allowance of a claim. *See Warner-Jenkinson*, 520 U.S. at 33; *Wong Labs., Inc. v Mitsubishi Elecs. Am., Inc.*, 103 F.3d 1571, 1578 (Fed. Cir. 1997); *Haynes Int'l, Inc. v. Jessop Steel Co.*, 8 F.3d 1573, 1577-78 (Fed. Cir. 1993).

B. **Patent Invalidity.**

1. **Burden of Proof and Presumption of Validity.**

The burden of proving invalidity rests with the party asserting it. "A patent, though presumed valid, 35 U.S.C. § 288 (1988), is actually a fragile entity, and must be propped

up by a myriad of supports, each representative of one of the legal requirements of validity. If even a single one of these supports is removed, the patent will fall. For example, a patent may be declared invalid . . . if it is rendered obvious by a combination of the prior art, *see id.* § 103; or if it fails to satisfy any one of a number of a variety of other conditions." *Morton Int'l Inc. v. Cardinal Chem. Co.*, 5 F.3d 1464, 1471-72 (Fed. Cir. 1993) (Mayer, J., concurring).

The statutory presumption of validity merely assumes the PTO properly did its job by considering all prior art or other evidence material to patentability. *See Lannom Mfg. Co. v. U.S. Int'l Trade Comm'n*, 799 F.2d 1572, 1575 (Fed. Cir. 1986). "[W]here the PTO has not considered facts relevant to an issue in suit, there is no reason to give deference to its action in issuing the patent and a court may find those facts controlling in determining whether the burden of proof has been sustained." *Kalman v. Kimberly-Clark Corp.*, 713 F.2d 760, 773 n.3 (Fed. Cir. 1983), *overruled on other grounds by SRI Int'l v. Matsushita Elec. Corp. of Am.*, 775 F.2d 1107 (Fed. Cir. 1985). Thus, "[t]he courts are the final arbiter of patent validity and, although courts may take cognizance of, and benefit from, the proceedings before the patent examiner, the question is ultimately for the courts to decide, without deference to the rulings of the patent examiner." *Quad Envtl. Techs. Corp. v. Union Sanitary Dist.*, 946 F.2d 870, 876 (Fed. Cir. 1991).

2. 35 U.S.C. § 103(a)—Obviousness.

A patent claim is invalid "if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. § 103(a). "The ultimate issue of obviousness turns on four factual determinations: (1) the scope and content of the prior art, (2) the level of ordinary skill in the art, (3) the differences between the claimed invention and the prior art, and (4) objective indicia of nonobvious." *Merck & Co. v. Teva Pharms. USA, Inc.*, 395 F.3d 1364, 1372-73 (Fed. Cir. 2005) (citation omitted).

When the question of obviousness depends on a combination of prior art references, there must be some teaching, suggestion, or motivation to combine the references. *See Pro-Mold & Tool Co. v. Great Lakes Plastics, Inc.*, 75 F.3d 1568, 1573 (Fed. Cir. 1996). Although the suggestion to combine references may flow from the nature of the problem, the suggestion more often comes from the teachings of the pertinent references, or from the ordinary knowledge of those skilled in the art that certain references are of special importance in a particular field. *Id.* Therefore, "[w]hen determining the patentability of a claimed invention which combines two known elements, 'the question is whether there is something in the prior art as a whole to suggest the desirability, and thus the obviousness, of making the combination.'" *In re Beattie*, 974 F.2d 1309, 1311-12 (Fed. Cir. 1992) (citation omitted).

Moreover, "[s]uch secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented. As indicia of obviousness or

nonobviousness, these inquiries may have relevancy." *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966) (citation omitted). However, the patentee must establish a causal relation or "nexus" between the purported invention and the secondary consideration, such as commercial success, to support a finding of non-obviousness. *See Merck*, 395 F.3d at 1376. In the context of a method-of-use patent for a prescription drug product, the Federal Circuit has explicitly rejected inferences of non-obvious drawn from the financial success of the invention where, for example, new chemical entity ("NCE") exclusivity or other patents precluded market entry by others. *See id.* at 1377 (holding that evidence of financial success is "weak" and "not significantly probative" to question of nonobvious where the product is protected by exclusive statutory rights that preclude market entry by others).

IV. The '863 Patent.

The PTO issued the '863 patent on August 8, 2000, to named inventors Paul Marie Victor Gillis and Valentin Florent Victor De Condé. According to the records of the PTO, Janssen Pharmaceutica N.V. ("Janssen") owns the '863 patent by assignment.

The '863 patent contains ten claims, which read as follows:

> 1. A tablet comprising as an active ingredient a therapeutically effective amount of galanthamine hydrobromide (1:1) and a pharmaceutically acceptable carrier, wherein said carrier comprises a spray-dried mixture of lactose monohydrate and microcrystalline cellulose (75:25) as a diluent, and an insoluble or poorly soluble cross-linked polymer disintegrant.
>
> 2. A tablet according to claim 1 wherein the disintegrant is crospolyvidone or croscarmellose.
>
> 3. A tablet according to claim 1 wherein the carrier further comprises a glidant and a lubricant.
>
> 4. A tablet according to claim 3 wherein the glidant is colloidal anhydrous silica and wherein the lubricant is magnesium stearate.
>
> 5. A tablet according to claim 1 comprising by weight based on the total weight:
>
> (a) from 2 to 10% galanthamine hydrobromide (1:1);
>
> (b) from 83 to 93% spray-dried mixture of lactose monohydrate and microcrystalline cellulose (75:25);
>
> (c) from 0.1 to 0.4% glidant;

(d) from 3 to 8% insoluble crosslinked polymeric disintegrant; and

(e) from 0.2 to 1% lubricant.

6. A tablet according to claim 5 comprising

(a) about 2 to 10% galanthamine hydrobromide (1:1);

(b) about 83 to 93% spray-dried mixture of lactose monohydrate and microcrystalline cellulose (75:25);

(c) about 0.2% colloidal anhydrous silica;

(d) about 5% crospolyvidone; and

(e) about 0.5% magnesium stearate.

7. A tablet according to claim 1 which is film-coated.

8. A tablet according to claim 7 wherein the film-coat comprises a film-forming polymer and a plasticizer.

9. A tablet according to claim 8 wherein the film-coat weighs from about 3% to about 8% of the uncoated tablet core.

10. A process of preparing a tablet according to claim 3 comprising the steps of:

(i) dry blending the active ingredient, the disintegrant and the optional glidant with the diluent;

(ii) optionally mixing the lubricant with the mixture obtained in step (i);

(iii) compressing the mixture obtained in step (i) or in step (ii) in the dry state into a tablet; and

(iv) optionally film-coating the tablet obtained in step (iii).

('863 patent at cols. 8-10.)

The commercial manufacture, use, sale, or offer for sale of Mylan's ANDA Product would not infringe any claim of the '863 patent, either literally or under the doctrine of equivalents.

A. No Literal Infringement of Claims 1-10.

The commercial manufacture, use, sale or offer for sale of Mylan's ANDA Product would not literally infringe claims 1-10 of the '863 patent.

Claim 1, the only independent claim, requires a tablet containing, among other things, galantamine hydrobromide, as the active ingredient, and a "diluent" or filler comprised of a "spray-dried mixture of lactose monohydrate and microcrystalline cellulose (75:25)." Claims 2-10 all depend, either directly or indirectly, on claim 1, and therefore incorporate all of the limitations from claim 1, including the particular diluent limitation. *See* 35 U.S.C. § 112. Thus, all claims require the tablet to contain a "diluent" made up of a "spray-dried mixture of lactose monohydrate and microcrystalline cellulose (75:25)." A "diluent" is a pharmaceutical excipient used as a diluting agent or filler in solid oral dosage forms, such as tablets and capsules. The term "spray-dried mixture" merely refers to a uniform combination of the two components that is created by spray drying, a well-known process that generally consists of "[a]tomization of a solution of one or more solids . . . followed by evaporation of the solvent from the droplets." *See, e.g.*, REMINGTON: THE SCIENCE AND PRACTICE OF PHARMACY 681 (Alfonso R. Gennaro *et al.* eds., 20th ed. 2000). The plain and ordinary meaning of claim 1 therefore requires that the claimed tablet contain a diluent made up of both 75% lactose monohydrate *and* 25% microcrystalline cellulose ("MCC") in a spray-dried mixture, such as MicroceLac®. Both components, as well as the spray-dried limitation, are critical to the claim.

The specification confirms this construction of claim 1. Prior art galantamine tablet formulations, according to the specification, contained mixtures of both lactose and MCC. ('863 patent at col. 2, lines 1-35.) The specification criticizes these formulations because: (1) the excipients separated during direct compression resulting in tablets with a variable composition (*id.* at col. 3, lines 14-17); and (2) the prior art formulations failed to achieve the required dissolution profile, namely, at least 80% dissolution in 30 minutes (*id.* at col. 3, lines 17-19). "In order to solve the perceived problems, the diluent was substituted for a spray-dried mixture of lactose monohydrate and microcrystalline cellulose (75:25), commercially available as Microcelac™." (*Id.* at col. 3, lines 19-23.) The specification repeatedly emphasizes this critical feature of the invention, stating that the required dissolution profile is "only met by using a particular diluent" consisting of "spray-dried mixture of lactose monohydrate and microcrystalline cellulose (75:25)." (*Id.* at col. 2, line 65 to col. 3, lines 1-8.) All descriptions and embodiments of the purported invention contain this "particular diluent." (*See, e.g., id.* at col. 1, lines 10-16; col. 3, lines 1-9; col. 3, lines 50-53; col. 5, line 29 to col. 6, line 56.) In sum, the specification clearly and unmistakably disavows tablets that do not contain this element. *See AstraZeneca*, 384 F.3d at 1340 ("Where the general summary or description of the invention . . . criticizes other products . . . that lack that same feature, this operates as a clear disavowal of these other products . . . .").

The prosecution history further confirms this interpretation. In the statement of reasons for allowance, the PTO examiner stated that "the prior art does not show nor fairly suggest applicants composition comprised of galanthamine hydrobromide (1:1) and a particular pharmaceutically acceptable carrier. The particular carrier combination of a spray dried mixture

of lactose monohydrate and microcrystalline cellulose (75:25) as a diluent and an insoluble or poorly soluble cross-linked polymer disintegrant enables the fast dissolution of said tablet." (3/11/00 Notice of Allowability at 2.)

Here, Mylan's ANDA Product does not contain or use any form of lactose and therefore also does not use a diluent made up of a spray-dried mixture of 75% lactose monohydrate and 25% MCC. Nor does Mylan's ANDA Product contain any spray-dried mixture of ingredients that function as a diluent.

For at least these reasons, the commercial manufacture, use, sale or offer for sale of Mylan's ANDA Product would not literally infringe claims 1-10.

B. No Infringement Under the Doctrine of Equivalents.

The manufacture, use, sale or offer for sale of Mylan's ANDA Product would not infringe claims 1-10 of the '863 patent under the doctrine of equivalents.

The differences between Mylan's ANDA Product and the product recited in the claims are substantial. The specification and prosecution history make clear that the special diluent is critical to the purported invention. Mylan's ANDA Product does not contain this critical limitation or anything that functions the same way. Moreover, the patentees cannot, as a matter of law, expand the scope of equivalents to encompass products that do not include the special spray-dried diluent where, as here, the patentees clearly criticized and disavowed such formulations in the specification. *See, e.g., AstraZeneca*, 384 F.3d at 1340, 1342 (holding that specification's clear disavowal of subject matter precludes the application of the doctrine of equivalents to recapture that subject matter); *SciMed*, 242 F.3d at 1341 (same). Application of the doctrine of equivalents to Mylan's ANDA Product also effectively would vitiate this diluent claim limitation altogether in violation of the "all elements" rule. *See Lockheed Martin*, 324 F.3d at 1321.

For at least these reasons, Mylan's ANDA Product would not infringe under the doctrine of equivalents.

V. The '527 Patent.

The PTO issued the '527 patent on March 19, 2002, to the same named inventors for the earlier '863 patent, Paul Marie Victor Gillis and Valentin Florent Victor De Condé. According to the records of the PTO, Janssen also owns the '527 patent by assignment. The '527 patent issued as a continuation of the application that eventually issued as the '863 patent. As such, with minor exceptions not relevant here, the specification of the '527 patent is identical to the specification of the '863 patent.

The '527 patent contains six claims, which read as follows:

> 1. A method of treating a disorder selected from dementia, mania or nicotine dependence in a patient in need thereof comprising administering to the patient a tablet comprising as an active ingredient a therapeutically effective amount of galanthamine hydrobromide (1:1) and a pharmaceutically acceptable carrier, wherein said carrier comprises a spray-dried mixture of lactose monohydrate and microcrystalline cellulose (75:25) as a diluent, and an insoluble or poorly soluble cross-linked polymer disintegrant.
>
> 2. The method of claim 1 wherein the disorder is dementia.
>
> 3. The method of claim 2 wherein the disorder is Alzheimer's dementia.
>
> 4. The method of claim 1 wherein the disorder is mania.
>
> 5. The method of claim 1 wherein the disorder is nicotine dependence.
>
> 6. A fast-dissolving galanthamine hydrobromide (1:1) tablet made by (i) dry blending the active ingredient, an insoluble or poorly soluble cross-linked polymer disintegrant and an optional glidant with a diluent comprising a spray-dried mixture of lactose monohydrate and microcrystalline cellulose (75:25); (ii) optionally mixing a lubricant with the mixture obtained in step (i); (iii) compressing the mixture obtained in step (i) or in step (ii) in the dry state into a tablet; and (iv) optionally film-coating the tablet obtained in step (iii).

('527 patent at col. 8.) Because the claims of the '527 patent are similar to, and not patentably distinct from, the issued claims of the '863 patent, the PTO allowed the claims of the '527 patent to issue only after Janssen terminally disclaimed any term of the '527 patent extending beyond the expiration of the '863 patent.

The manufacture, use, sale or offer for sale of Mylan's ANDA Product would not infringe any claim of the '863 patent, either literally or under the doctrine of equivalents.

A. No Literal Infringement of Claims 1-6.

Claim 1 is a method-of-use claim that claims a method of treating dementia, mania or nicotine dependence, by administering a tablet containing galantamine hydrobromide and, among other things, the same particular diluent from the '863 patent comprised of "a spray-

dried mixture of lactose monohydrate and microcrystalline cellulose (75:25)." Dependent claims 2-5 all depend, either directly or indirectly, on claim 1, and therefore incorporate all of the limitations from claim 1, including the special diluent limitation. *See* 35 U.S.C. § 112.

As an initial matter, Mylan would not directly infringe claims 1-5 because Mylan does not treat or administer drugs to patients, and would not directly use or administer galantamine for the purpose of treating or preventing any of the claimed disorders. *See Warner-Lambert Co. v. Apotex Corp.*, 316 F.3d 1348, 1363 n.7 (Fed. Cir. 2003).

Mylan would not induce or contribute to infringement of claims 1-5 for at least the same reasons that Mylan would not literally infringe claims 1-10 of the '863 patent (*see* section IV.A, above), which reasons are fully incorporated by reference herein. Specifically, claims 1-5 all require the use of a special diluent comprised of "a spray-dried mixture of lactose monohydrate and microcrystalline cellulose (75:25)." For the same reasons discussed in section IV.A, above, properly construed, claims 1-5 require both 75% lactose monohydrate *and* 25% MCC in a spray-dried mixture, and necessarily exclude tablets that lack these critical elements. Mylan's ANDA Product contains neither lactose nor a spray-dried mixture of 75% lactose monohydrate and 25% MCC, or any equivalent spray-dried mixture of ingredients that function as a diluent.

Claim 6, while drafted as a product-by-process claim, requires a tablet with the same diluent limitation of claims 1-5, namely, "a spray-dried mixture of lactose monohydrate and microcrystalline cellulose (75:25)." Mylan's ANDA Product does not contain such a mixture or any equivalent thereof.

For at least these reasons, the commercial manufacture, use, sale or offer for sale of Mylan's ANDA Product would not literally infringe claims 1-6 of the '527 patent.

B. No Infringement Under the Doctrine of Equivalents.

The manufacture, use, sale or offer for sale of Mylan's ANDA Product would not infringe claims 1-6 of the '827 patent under the doctrine of equivalents for the same reasons that Mylan would not infringe the '863 patent as set forth in section IV.B, above, which reasons are respectfully incorporated by reference herein.

Specifically, the differences between Mylan's ANDA Product and the product recited in the claims are substantial. The specification and prosecution history make clear that the special diluent is critical to the purported invention. Mylan's ANDA Product does not contain this critical limitation or anything that functions the same way. Moreover, the patentees cannot, as a matter of law, expand the scope of equivalents to encompass products that do not include the special spray-dried diluent where, as here, the patentees clearly criticized and disavowed such formulations in the specification. *See, e.g., AstraZeneca*, 384 F.3d at 1340, 1342 (holding that specification's clear disavowal of subject matter precludes the application of the doctrine of equivalents to recapture that subject matter); *SciMed*, 242 F.3d at 1341 (same). Application of the doctrine of equivalents to Mylan's ANDA Product also effectively would

vitiate this diluent claim limitation altogether in violation of the "all elements" rule. *See Lockheed Martin*, 324 F.3d at 1321.

Lastly, during prosecution of the '527 patent, the patentees distinguished their tablet from prior art galantamine compositions containing just starch or lactose on the ground that such prior art did not contain a diluent comprised of a "spray-dried mixture of lactose monohydrate and microcrystalline cellulose (75:25)." (3/7/01 Amendment and Remarks at 2-3.) Such arguments and representations, made to obtain allowance of the claims, now estop the patentees from asserting a range of equivalents that would include compositions that do not contain the claimed diluent.

For at least these reasons, Mylan's ANDA Product would not infringe under the doctrine of equivalents.

VI. The '318 Patent.

The PTO issued the '318 patent on May 5, 1987, to named inventor Bonnie Davis, who filed the original application on January 15, 1986. According to the records of the PTO, Synaptech Inc. owns the '318 patent by assignment.

A. Claims.

The '318 patent contains seven claims, which read as follows:

1. A method of treating Alzheimer's disease and related dementias which comprises administering to a patient suffering from such a disease a therapeutically effective amount of galanthamine or a pharmaceutically-acceptable acid addition salt thereof.

2. A method according to claim 1, wherein the administration is parenteral at a daily dosage of 5-1,000 mg of galanthamine or a pharmaceutically-acceptable acid addition salt thereof.

3. A method according to claim 2, wherein said dosage rate is 50-300 mg per day.

4. A method according to claim 1, wherein said administration is oral and is in the range 10-2000 mg per day.

5. A method according to claim 4, wherein said dosage rate of 100-600 mg per day.

6. A method according to claim 1, wherein galanthamine is administered at a dosage rate of 0.1 to 4 mg/kg body weight of a patient, parenterally.

7. A method according to claim 1, wherein galanthamine is administered intracerebroventricularly via an implanted reservoir at a dosage rate of 0.01 to 5.0 mg/kg day.

('318 patent at cols. 3-4.)

B. Invalidity of Claims 1-7.

Claims 1-7 are invalid for obviousness under 35 U.S.C. § 103(a) in view of at least the following prior art references:

- Blaine S. Greenwald *et al.*, *Neurotransmitter Deficits in Alzheimer's Disease: Criteria for Significance*, 31 J. AM. GERIATRICS SOC'Y 310-16 (May 1983) (hereinafter, "Greenwald");
- D.A. Cozanitis, *Galanthamine Hydrobromide, a Longer Acting Anticholinesterase Drug, in the Treatment of the Central Effects of Scopolamine (Hyoscine)*, 26 ANAESTHESIST 649-50 (1977) (hereinafter, "Cozanitis");
- L.J. Thal *et al.*, *Oral Physostigmine and Lecithin Improve Memory in Alzheimer Disease*, 13 ANNALS OF NEUROLOGY 491-96 (1983) (hereinafter, "Thal"); and
- L.N. Nesterenko, *Influence Exerted by Galantamine on the Acetylcholinesterase Activity*, 28 FARMAKOL TOKSIKOL 413-14 (1965) (hereinafter, "Nesterenko").

The patentee did not cite, and the PTO examiner did not consider, any of these references, all of which were publicly available prior to January 15, 1985, and therefore constitute prior art under 35 U.S.C. § 102(b).

1. Scope and Content of the Prior Art.

The '318 patent addresses the problem of treating Alzheimer's disease ("AD") and related dementias by using galantamine or its salts. The prior art described below, all of which predates the alleged invention by at least several years, addresses the same problem and field of the purported invention. Based on these references alone, a person of ordinary skill in the art of medicinal chemistry in 1985 would have immediately recognized and reasonably expected that galantamine would be useful for the treatment of AD.

(a) Greenwald.

Greenwald addresses the state of the art in the pharmacological investigation of AD in the early 1980s, and concludes that "any pharmacotherapy of Alzheimer's disease will ultimately have to address the *cholinergic deficit*." (Greenwald at 314) (emphasis added). By way of background, the term "cholinergic" refers to nerve cells or fibers that employ "acetylcholine," a particular neurotransmitter that conducts messages throughout the brain. "Acetylcholinesterase," otherwise known as "AChE," is an enzyme (or cholinesterase) that breaks down and deactivates the neurotransmitter acetylcholine, thus decreasing acetylcholine levels. An "anticholinesterase" drug selectively inhibits AChE, thereby increasing the level of acetylcholine in the brain. Greenwald identifies the "*cholinergic deficit*," or a deficiency in the neurotransmitter acetylcholine, as the main problem to be addressed by any drug therapy for treating AD through the use of an anticholinesterase (or AChE inhibiting) drug.

Greenwald reaches this conclusion by developing criteria for determining the role of various neurotransmitters in AD. According to Greenwald, "*[t]he evidence that cholinergic activity is decreased in brain regions implicated in the symptomatology of AD is overwhelming*. Reductions in . . . acetylcholinesterase (AChE) are most substantial in the hippocampus and frontotemporal cortices." (Greenwald at 311) (emphasis added). Greenwald explains:

> In over 200 brains from patients in whom a careful diagnosis of AD had been established, a large number of investigators have confirmed a cholinergic deficit. Further clarification and substantiation of a cholinergic deficit in the brains of patients with AD derives from recent work documenting a reduction in cholinergic neuron counts of up to 80 per cent . . . . in brains affected by AD, compared with controls. . . . In comparison to other neurotransmitters, only a cholinergic deficit is consistently present in those brain regions that are the likely source of AD symptomatology.

(*Id.*) (citations omitted).

Greenwald further explains that pharmacologic manipulation of central cholinergic activity demonstrated a significant and reproducible effect on learning and memory. (Greenwald at 312.) Specifically, Greenwald notes that administration of an anticholinergic drug called scopolamine, which acts against the cholinergic system and decreases acetylcholine levels, produced memory and cognitive deficits in normal young adults that were "markedly similar" to the same symptoms in aged subjects with AD. But "[p]hysostigmine, *an anticholinesterase and pharmacologic antagonist of scopolamine*, improved the memory and cognitive dysfunction produced by scopolamine . . . ." (*Id.*) (emphasis added)

In fact, Greenwald reports that the *anticholinesterase* drug physostigmine both enhanced learning in normal young subjects and partially reversed the learning deficit of AD patients. (Greenwald at 313.) Moreover, as Greenwald discloses, "[t]etrahydroaminoacridine (THA), a longer-acting acetylcholinesterase inhibitor, has produced global improvements in AD patients. (*Id.*) Greenwald concludes that, with respect to AD, "only cholinergic drugs fulfill the pharmacologic criteria: anticholinergic agents [like scopolamine] produce a 'dementia' that mimics the memory/cognitive abnormalities seen in AD; and cholinomimetics [like AChE inhibitors that increase acetylcholine levels] partially improve memory in normal subjects and AD patients" (*Id.*)

In other words, Greenwald teaches a person of ordinary skill in the art of medicinal chemistry to treat AD and related symptoms by improving the cholinergic or acetylcholine deficiency through the use of an AChE inhibiting drug.

(b) Cozanitis.

Cozanitis specifically identifies galantamine hydrobromide, the salt of galantamine currently marketed as Reminyl®, as a superior drug for combating anticholinergic effects. In particular, Cozanitis teaches that galantamine hydrobromide is an *anticholinesterase* drug capable of penetrating the blood brain barrier and acting centrally as well as peripherally. (Cozanitis at 649.) Cozanitis further suggests that galantamine hydrobromide would be useful to combat the central anticholinergic (or acetylcholine-lowering) effects of scopolamine (*Id.*)—the anticholinergic drug identified by Greenwald, above, that acts against the cholinergic system by decreasing acetylcholine levels and producing the memory and cognitive deficits seen in patients with AD.

Notably, Cozanitis states that physostigmine, another well-known anticholinesterase drug (discussed in Greenwald above) is currently used to combat the central effects of anticholinergic drugs like scopolamine, but that relapses are common because of its brevity of action. Based on studies using 20 mg intravenous doses of galantamine hydrobromide (for an individual of 60 kg body weight), Cozanitis concludes galantamine hydrobromide is superior to physostigmine because it is longer lasting in its central effects, noting that plasma cortisol levels remained raised six hours after galantamine hydrobromide had been given to patients who had undergone general anesthesia. (Cozanitis at 649-50).

In sum, Cozanitis not only identifies galantamine hydrobromide as an effective anticholinesterase drug capable of penetrating the blood brain barrier and achieving a sustained increase in acetylcholine levels, just as Greenwald suggested for treating AD, but Cozanitis further discloses that galantamine is superior to other drugs in the same class.

(c) Thal.

Thal conducted an empirical study on patients with AD, which correlated the degree of improvement in memory with the amount of physostigmine, a well known selective

inhibitor of AChE. (Thal at 491, Abstract). Thal confirms that a cholinergic deficiency is characteristic of AD and memory loss. (*Id.*) For example, Thal demonstrates that administration of scopolamine, a centrally acting agent that decreases acetylcholine levels, causes marked impairment in the ability to learn new material, or memory impairment similar to that observed in normal aging. (*Id.*) Oral administration of physostigmine, a well known selective inhibitor of AChE, reverses scopolamine-induced dementia. (*Id.*) Thal further demonstrates that orally administered physostigmine improves memory in AD patients, and concludes that this effect is directly due to enhancement of the cholinergic system. (*Id.* at 494.) Thal reports that the optimal individual oral dose was either 2.0 or 2.5 mg physostigmine, administered 4-5 times per day, for each patient. (*Id.*)

In sum, Thal teaches that dementia and memory impairment associated with AD are due to a cholinergic deficiency; that such impairment could be reversed by using a selective inhibitor of AChE; and that oral administration of physostigmine, a well known AChE inhibitor, in 2 mg or 2.5 mg doses 4-5 times per day improves memory in AD patients.

(d) Nesterenko.

Nesterenko expressly teaches that galantamine inhibits or depresses AChE activity in different parts of the brain with the degree of inhibition contingent upon the amount of the dose. Nesterenko specifically compared the AChE inhibitory effects with those of physostigmine (also known as eserine). Nesterenko concludes and teaches that the nature of the anticholinesterase activity produced in the various parts of the brain by galantamine and physostigmine did not materially differ. However, Nesterenko reports that galantamine needed to be administered in doses 10-12 times greater than physostigmine to produce the same degree of central acetylcholinesterase inhibition. (Nesterenko at 414).

2. Comparison of the Claimed Invention and the Prior Art.

A comparison between the claimed invention and the prior art demonstrates that claims 1-7 would have been obvious to a person of ordinary skill in the art of medicinal chemistry in 1985 based on the prior art described above.

Claim 1, the only independent claim, covers a method of treating AD with galantamine or its salts. The specification of the '318 patent describes AD as characterized by a "cortical cholinergic deficiency" that causes behavioral deficits, including an "inability to learn and retain new information." ('318 patent at col. 2, lines 47-53.) The specification then concludes that "[d]rugs that can normalize these abnormalities [*i.e.*, such as memory loss characterized by a cholinergic deficiency] would have a reasonable expectation of efficacy in Alzheimer's disease." (*Id.* at col. 2, lines 52-54 (citation omitted).)

For the prior art to render claim 1 obvious, all that is required is a suggestion or motivation to use galantamine for the treatment of AD, together with a reasonable expectation of success. *See SIBIA Neurosciences, Inc. v. Cadus Pharm. Corp.*, 225 F.3d 1349, 1356 (Fed. Cir. 2000). "There was no great leap required of those skilled in the art to" reach that conclusion

here. *See Merck*, 395 F.3d at 1373. Greenwald directly addresses the same problem as the '318 patent: the treatment of AD. To that end, Greenwald teaches a person of ordinary skill in the art to treat AD by using a drug that addresses the cholinergic deficiency likely responsible for AD and its symptoms. Drugs like physostigmine, an anticholinesterase (or AChE inhibitor) and pharmacologic antagonist of the anticholinergic effects of scopolamine, partially reverse the learning and memory deficits in AD patients. Greenwald therefore concludes that, as of 1983, only cholinergic or *anticholinesterase* drugs that are capable of reversing the anticholinergic effects of drugs like scopolamine fulfill all of the pharmacological criteria for treating AD.

Greenwald already identifies physostigmine as a useful anticholinesterase (or AChE inhibitor) drug for treating AD. But as the specification of the '318 patent concedes, galantamine and its salts also "have, for many years, been known to have anticholinesterase properties." ('318 patent at col. 1, lines 11-13.) Cozanitis expressly teaches that galantamine hydrobromide not only combats the anticholinergic effects of scopolamine, just as physostigmine does, but that galantamine is superior to physostigmine because it is longer lasting.

The combination of these two references, motivated by the Greenwald suggestion to treat AD by targeting cholinergic drugs that selectively inhibit AChE, clearly suggests to a person of ordinary skill in the art of medicinal chemistry both the application of galantamine hydrobromide for the treatment of AD and a reasonable expectation of success. Thus, claim 1 is obvious in view of at least Greenwald and Cozanitis, which disclose a method of treating AD and related memory disorders comprising the administration of an effective amount of galantamine hydrobromide.

The same reasoning applies to claims 2-7, which depend from claim 1 and merely add additional dosing and administration limitations, including: parenteral administration at a dosage of 5-1,000 mg per day (claim 2); parenteral administration at a dosage of 50-300 mg per day (claim 3); oral administration at a dosage in the range of 10-2000 mg per day (claim 4); oral administration at a dosage in the range of 100-600 mg per day (claim 5); parenteral administration at a dosage of 0.1 to 4 mg/kg (claim 6); and intracerebroventricular administration via an implanted reservoir at a dosage rate of 0.01 to 5.0 mg/kg per day (claim 7). These additional limitations do not render claims 2-7 patentably distinct from claim 1.

As an additional matter, the specification provides no basis for selecting any particular route of administration or dosage. Moreover, the claimed routes of administration are well-known and therefore obvious to a person of ordinary skill in the art based on the prior art. For example, Cozanitis expressly discloses parenteral administration of galantamine hydrobromide, and Thal teaches oral administration of acetylcholinesterase inhibitors.

The prior art also renders the claimed dosages obvious. Thal teaches oral dosage rates of 3 to 16 mg per day for physostigmine for the treatment of AD patients. Nesterenko

specifically discloses that galantamine should be administered in doses 10-12 times greater than for physostigmine in order to produce the same degree of central AChE inhibition. Together, these references teach the administration of approximately 30 to 190 mg galantamine hydrobromide per day. This range overlaps the respective ranges recited in claims 2-5. In addition, for a patient of average weight (*i.e.*, 150 lbs. or 68 kg), the daily dosage of 30 to 190 mg/day is equivalent to about 0.4 to 2.8 mg/kg per day. This range clearly overlaps those recited in claims 6-7, as would ranges based on body weights greater than or less than 150 lbs.

For at least these reasons, claims 1-7 are obvious in view of the prior art not considered by the PTO examiner.

3. **Secondary Considerations.**

Secondary considerations do not render the claims non-obvious. Even assuming that Janssen's commercial product Reminyl® embodies the claimed invention, no causal relation or "nexus" exists between the claimed invention and the financial success, if any, of Reminyl®. The financial success of Reminyl® is attributable solely to Janssen's extensive marketing efforts and the NCE exclusivity that prohibited marketing by others for at least five (5) years, and not the claimed invention. As the Federal Circuit recently held, such evidence is "weak" and "not significantly probative" of non-obvious. *See Merck*, 395 F.3d at 1376-77.

Nor can the patentee establish any unexpected results or long felt but unmet need in the alleged invention. The patentee admittedly did not obtain any experimental results, much less unexpected ones, before filing the original patent application. (*See* 9/9/86 Amendment and Response at 2.) Rather, the patentee clearly expected the invention to work for its intended purpose based on the prior art alone. That prior art provides the solution to the problem addressed by the '318 patent.

For at least these reasons, claims 1-7 of the '318 patent are invalid for obviousness under 35 U.S.C. § 103(a)

* * *

Mylan reserves all rights to raise any additional defenses relating to invalidity, unenforceability, and noninfringement.

CERTIFICATE OF SERVICE

I hereby certify that on the 21st day of February, 2006, the attached **NOTICE OF DEPOSITION UNDER FED. R. CIV. P. 30(b)(6) TO MYLAN PHARMACEUTICALS INC. AND MYLAN LABORATORIES, INC.** was served upon the below-named counsel of record at the address and in the manner indicated:

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